Suicide Risk in Substance Abuse Treatment Clinical Trials; Is Adverse Event Reporting Alone Sufficient?

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Suicide Risk in Substance Abuse Treatment Clinical Trials

- Scope of the problem
- Evaluation of safety data
- The National Institute on Drug Abuse National Drug Abuse Treatment Clinical Trial Network (NIDA CTN)
- Analysis of two completed trials
- Individual case reviews
- Future reporting strategies
Evaluation of Safety Data

Pre-specified safety events
– High importance, specific data collection tool, higher quality data, increases reliability and reproducibility

Adverse events
– High importance, low quality data, subjective, difficult to reproduce,
  - Limited information regarding protocol, CRFs, site quality and variability
  - Even more limited with postmarketing reports
NIDA CTN

- 27 completed clinical trials
- 23 posted on the CTN data share
  - [http://www.ctndatashare.org/](http://www.ctndatashare.org/)
  - Protocol, case report forms, de-identified data
Two completed trials


Safety Reporting
CTN0009 and CTN0029

- Standard adverse event reporting
- Also used the Beck’s Depression Inventory assessment
  - 23 item self assessment
  - 9th assessment
    - I don't have any thoughts of killing myself
    - I have thoughts of killing myself but would not carry them out
    - I would like to kill myself
    - I would kill myself if I had the chance
# Results

## Adverse Events

<table>
<thead>
<tr>
<th>Protocol</th>
<th>Total</th>
<th>CTN-0009 (SUD)</th>
<th>CTN-0029 (Non-SUD)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>N</td>
<td>%</td>
<td>N</td>
</tr>
<tr>
<td>Total</td>
<td>480</td>
<td>100.0</td>
<td>225</td>
</tr>
<tr>
<td>Adverse Events</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>SUICIDE ATTEMPT</td>
<td>1</td>
<td>0.2</td>
<td>1</td>
</tr>
<tr>
<td>DEPRESSION SUICIDAL</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>SUICIDE IDEATION (3 events in 2 individuals)</td>
<td>2</td>
<td>0.4</td>
<td>1</td>
</tr>
<tr>
<td>NO SUICIDE RELATED ADVERSE EVENT</td>
<td>476</td>
<td>99.2</td>
<td>222</td>
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</table>
# Results
## Beck’s Depression Inventory

<table>
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<tr>
<th>BDI Suicidal Thoughts or Wishes baseline or follow-up</th>
<th>Total</th>
<th>Protocol</th>
</tr>
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<tbody>
<tr>
<td></td>
<td>N</td>
<td>%</td>
</tr>
<tr>
<td>I WOULD LIKE TO KILL MYSELF</td>
<td>3</td>
<td>0.6</td>
</tr>
<tr>
<td>I HAVE THOUGHTS OF KILLING MYSELF, BUT I WOULD NOT CARRY THEM OUT</td>
<td>82</td>
<td>17.1</td>
</tr>
<tr>
<td>I DON'T HAVE ANY THOUGHTS OF KILLING MYSELF</td>
<td>395</td>
<td>82.3</td>
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70 of 85 positive responses noted in CTN0009 the SUD population (82.4%)
### Results

#### Beck’s Depression Inventory

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Results

Individual Subjects

- Adverse events
  - Four subjects reported five suicidality events.

- BDI
  - Three subjects on endorsed wanting to “kill myself”
Four Subjects, Five Reported Events and BDI Response

- 09_0224401: AE: Suicidal ideation Day 90
- 09_058256: SAE: Depression Suicidal Day 47
- 09_080608: SAE: Suicidal attempt Day 90
- 29_013343: AE: Suicidal ideation Day 64
Three BDI Responses to “kill myself” and AE Reports

09_037318

BDI Response
I would like to kill myself
I have thoughts of killing myself, but I would not carry them out
I don’t have any thoughts of killing myself

AE: Pain in Extremity Day 36
AE: Depression AE: Insomnia Day 75
AE: Eye Pruritus Day 34
AE: Hypoesthesia Day 62

Baseline Day 33 Day 62 Day 99 Day 188

09_069727

BDI Response
I would like to kill myself
I have thoughts of killing myself, but I would not carry them out
I don’t have any thoughts of killing myself

Baseline

09_071707

BDI Response
I would like to kill myself
I have thoughts of killing myself, but I would not carry them out
I don’t have any thoughts of killing myself

AE: Abdominal pain Day 25
AE: Dizziness Day 15

Baseline Day 36 Day 109 Day 191
Future Reporting Strategies
FDA Recommendations

- Prospective suicidality assessments
  - All clinical trials involving any drugs being developed for any psychiatric indications
  - All antiepileptic drugs
  - Neurologic drugs with central nervous system (CNS) activity
  - Consider
    - isotretinoin and other tretinoins
    - beta blockers (especially those entering the brain), reserpine
    - drugs for smoking cessation
    - drugs for weight loss
Future Reporting Strategies
Substance Use Disorder (SUD)

Because SUD is a high risk population

- Implement a suicide assessment tool in all SUD trials with CNS pharmacologic intervention
- Consider implementation in all SUD
Acknowledgements

- Paul Van Veldhuisen, Ph.D.¹
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- Steve Sparenborg, Ph.D.²
- Carmen Rosa, MS²

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2 – NIDA CCTN

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EXTRA SLIDES
FDA Coding of Events

- FDA has adopted the C-CASA as the standard for coding suicidality data.
  1. Completed Suicide
  2. Suicide Attempt
  3. Preparatory Actions Toward Imminent Suicidal Behavior
  4. Suicidal Ideation
  5. Self-Injurious Behavior Intent Unknown
  6. Fatal Event: Not Enough Information
  7. Self-Injurious Behavior Without Suicidal Intent
  8. Other (Accident, Psychiatric, Medical)
  9. Nonfatal Event: Not Enough Information
FDA Guidance

As prospective assessments for suicidality are adopted, certain of these codes become irrelevant for patients who can be assessed.

Codes 1 to 4 are the events that the FDA considers to represent *suicidality*, and these are the events that would be likely to be included in any subsequent meta-analyses.

Code 7 represents a nonsuicidal event, but should nevertheless be captured because it has some predictive value for future suicidality, and might be useful for certain analyses.

Codes 5, 6, and 9 are indeterminate categories, and are unnecessary for prospectively assessed patients. Any deaths in a clinical trial would of course be explored with sufficient depth to determine, if possible, whether or not they should be classified as suicides, and this information would be captured on the assessment form. If they remain indeterminate, there is no need to code the information. Similarly, any self-injurious behaviors and suspicious accidents would be explored as part of the prospective assessment. Again, if such events remain indeterminate, there is no need to code the information.

Events that would code to 8 (e.g., events that represent accidents, psychiatric, or other medical events) need not be captured.
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